SUPPLEMENTAL MATERIAL

Morning plasma cortisol as a cardiovascular risk factor: findings from prospective cohort and Mendelian randomization studies

Supplemental Methods

The Northern Sweden VIP, MONICA and MSP studies

Cases were identified by cross linkage between the MONICA myocardial infarction (MI) and stroke registries and the survey cohorts (VIP, MONICA and MSP), and controls from the survey cohorts were matched for sex, age, survey type and date of survey.

VIP is an ongoing community intervention program targeting cardiovascular disease and diabetes prevention.[1] Participants are asked to participate in a health survey at their primary health centre at the ages of 30, 40, 50, and 60 years. However, those aged 30 are no longer invited because of a lack of resources. The participation rate was initially 55% but has increased and is now approximately 65%. The total number of unique individuals surveyed in VIP was 99,268 as of 31 December 2014.

MONICA consists of randomly selected individuals aged 25–74 years from the counties of Västerbotten and Norrbotten who were invited to participate in a health study. The study has been repeated seven times at approximately 5-year intervals with new random samples of 2500 individuals each (the first two surveys invited 2000 individuals each).[2] For each survey 250 men and 250 women from each 10-year age group were randomly sampled from population registers, stratified for age and sex. The overall participation rate was 74%, and a total of 12,368 unique persons had participated by 31 December 2014.

Data for the MSP cohort, consisting of 28,778 women, were collected between 1995 and 2006 when the women attended their regular mammography examination and were asked to donate blood samples for research. In addition, anthropometric measurements were taken.

In all studies, participants were asked to donate blood to be stored at -80°C for future research. Participants were fasting before sampling for a minimum of 4 hours (extended to 8 hours in 1992).

Since 1985, all (in-hospital and out-of-hospital) cases with acute stroke (in the age group 25–74 years) and acute MI (in the age group 25–64 years) in the MONICA area (i.e., Västerbotten and Norrbotten) have been included in the Northern Sweden MONICA registries using WHO criteria and MONICA methodology. Possible CVD events (fatal and non-fatal CVD (MI or stroke)) were identified through screening of hospital discharge records, general practitioners' reports, and death certificates, with ICD 8 and 9 codes 410-413 and 430-438 corresponding to ICD 10 codes I20-I24 and I60-69. For death certificates, the codes 414 and 798–799 (ICD 8 and 9), and I25 and R96–99 (ICD 10) were also included. Data collection included information on medical history, symptoms, examinations, presenting electrocardiogram (ECG), and stroke subtypes. The number of subjects with MI and stroke included in the Northern Sweden MONICA registry not willing to participate in further studies has averaged two to six per year (0.2–0.6 %).

Detailed descriptions of criteria for diagnosis of stroke and classification of subtypes have been published.[3,4] In short, stroke cases were classified into one of the categories "definite stroke", "unclassified stroke", or "no stroke". Unclassified events were mostly fatal cases with a death certificate diagnosis of stroke where information on previous history of stroke or of the clinical event was not obtainable. In this study, only cases classified as "definite stroke" have been included in nonfatal events. In fatal events, the category "unclassifiable stroke" has also been included, in accordance with the agreed convention in the core MONICA project.

British Women's Heart and Health Study (BWHHS)

Women from the main cohort with CHD at baseline (N = 694 prevalent cases; 16.2%) were excluded. Incident cases of CHD (169 cases, 111 non-fatal and 58 fatal) were identified by two-yearly medical record reviews and through routine death registration until October 2016, defined as either of: (i) death with an underlying or contributing cause of CHD (ICD10 codes I20-I25, I51.6); or (ii) a MI (defined according to WHO criteria), first diagnosis of angina or coronary artery by-pass or angioplasty. For each case, two controls were randomly selected, within 5-year age groups of the cases, from women without CHD at the baseline assessment and who

had been followed-up over the same time period as the cases without experiencing a CHD event. Additional controls were selected to replace those who subsequently died or experienced a CHD event within 1 year of the selection.

Additional analyses of prospective cohort studies

Additional analyses were performed to investigate whether the effect of cortisol on CVD differed by sex. Similarly, the outcome was stratified to investigate the effect of cortisol on CHD and stroke separately. The equality of coefficients from these stratified analyses were formally tested using the generalized Hausman specification test.[5]

Methods for dealing with missing data

In order to increase efficiency and minimise selection bias we used multivariate multiple imputation to impute missing data for potential confounders including all exposures, covariables, outcomes and potential predictors of missing data in the imputation equations.[6] This assumes the missing data can be explained by the observed data (missing at random assumption).[7] It is not possible to test this assumption, but we have included all exposures, outcomes, covariables and any variables that are predictive of missing data in our imputation models in order to increase the plausibility that it is correct. Table S6 lists the variables included in these missing data prediction models and how they were entered into the models. In Stata, we carried out 20 cycles of regression switching as described by Royston[6] and generated 20 imputation datasets. The multiple imputation approach creates a number of copies of the data (in this case, 20 copies) in which missing values are imputed, with an appropriate level of randomness, by chained equations. The average estimate from each of these 20 datasets is obtained using Rubin's rules taking account of the uncertainty in the imputation so that the standard errors for any regression coefficients (used to calculate p-values and 95% confidence intervals) take account of uncertainty in the imputations as well as uncertainty in the estimate.

Multivariable regression of prospective studies meta-analysis

The Caerphilly study includes 2512 men (2323 with cortisol data) from the town of Caerphilly or surrounding villages examined between 1979 and 1983.[8] The majority of fasting blood samples were taken between 0700h and 0800h. The records of all men at the National Health Service Central Registry were flagged so that notification of death was automatic and a copy of the death certificate was received. Fatal ischaemic heart disease (IHD) events were classified as deaths with International Classification of Diseases 9 (ICD-9) codes 410 to 414. Non-fatal IHD events were ascertained through follow-up clinics and discharges from local hospitals with a diagnosis code of ICD-9 410 to 414.

The Vietnam Experience study consists of 18313 male former military personnel (4255 with cortisol data)[9]. All fasting blood samples were taken in the morning. Mortality due to CVD was classified using ICD-9 codes: 390–434 and 436–448, and ICD-10 codes: I00–I78. The majority of deaths were from IHD.

Sensitivity analyses of the multivariable regression of prospective studies meta-analysis

We undertook a leave one out analysis, in which the meta-analysis was repeated four times with one study removed each time, to explore whether any differences between study results importantly influenced the pooled estimate. To assess potential small study bias, a funnel plot was prepared of ln*OR* against the standard error ln*OR*[10] and analysed using Egger's test.[11]

One-sample Mendelian randomization

The causal estimate was derived using the two-stage method comprising a first-stage regression of the exposure on the SNP, and a second-stage regression of the outcome on the fitted values of the exposure from the first stage. As cortisol measurements were taken at baseline (prior to onset of CVD) then the first stage (SNP-cortisol) association was obtained using cases and controls.[12] . We included covariates in the first-stage and second-stage regressions. This increases efficiency and hence the precision of the causal estimate. However, it may lead to bias in the causal estimate if a covariate is on the causal pathway between exposure and outcome or is a collider or causally downstream of a collider.[13]

Two-sample Mendelian randomization

This approach assumes that the gene-exposure and gene-outcome associations are estimated in non-overlapping samples and are representative of the same population (similar age, sex distribution and the same ethnic group).[18] For our analyses there are no studies that contributed to both CORNET and CARDIoGRAM and so we can rule out a large overlap. A proportion of participants of the ORCADES study, which contributed to CORNET, were eligible to participate in UK Biobank. We are unable to rule out the possibility that individuals may have participated in multiple studies and so may have contributed to CORNET and to CARDIoGRAM or UK Biobank. If this is the case then estimates from the two-sample Mendelian randomization analyses may be biased towards the estimate obtained from conventional methods (e.g. multivariable regression).[19]

We ran three additional analyses: first, a weighted median approach[14] which is consistent even when up to half of the information comes from invalid instrumental variables; second, a maximum likelihood[15] approach which uses linear relationship between the risk factor and outcome and a bivariate normal distribution for the genetic association estimates; finally, inverse variant weighting (IVW) to combine each of the three SNPs which is a linear regression analysis through the mean SNP-exposure and SNP-outcome results that is forced to go through zero (i.e. constrained to have intercept zero).[16] As a sensitivity analysis to explore horizontal pleiotropy we used MR-Egger regression[16], which is similar to IVW but does not constrain the regression line to go through zero. A non-zero intercept in MR-Egger suggests possible horizontal pleiotropy; the slope can be interpreted as the effect having relaxed the horizontal pleiotropy assumption. To investigate how pleiotropy might be influencing our estimates we performed multivariable Mendelian randomization[17] which uses multiple genetic variants associated with more than one risk factor to simultaneously estimate the causal effect of each of the risk factors on the outcome.

Supplemental References

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Supplemental Tables

Table S1. Association of plasma cortisol with CVD in the combined VIP, MONICA and MSP cohort and BWHHS cohort with the same individuals in each model

	VIP, MONICA and MSP				BWHHS			
	Cases	Controls	OR (95% CI)	p	Cases	Controls	OR (95% CI)	p
Unadjusted	323	492	1.16 (0.99 to 1.35)	0.07	154	313	0.95 (0.78 to 1.16)	0.78
Adjusted	323	492	1.19 (1.01 to 1.41)	0.04	154	313	0.99 (0.80 to 1.22)	0.92
Unadjusted and 0700h-1100h	268	396	1.19 (0.99 to 1.43)	0.06	45	89	1.21 (0.80 to 1.83)	0.36
Adjusted and 0700h-1100h	268	396	1.31 (1.07 to 1.60)	0.009	45	89	1.13 (0.72 to 1.76)	0.59

OR, odds ratio; CI, confidence intervals; p, p value. All models included the matching variables of age; for VIP, MONICA and MSP, all models included the matching variables of sex, study, and baseline assessment date. Adjusted models also included BMI, smoking and time of sampling in the regression models. Analyses were repeated restricted to individuals with blood sampling time between 0700h and 1100h.

Table S2. Effect of including each confounder one-at-a-time on the associations of plasma cortisol with CVD in the combined VIP, MONICA and MSP cohort and BWHSS cohort with the same individuals in each model

	VIP, MONICA and MSP				BWHHS			
	Cases	Controls	OR (95% CI)	p	Cases	Controls	OR (95% CI)	p
All sampling times included:								
Unadjusted	323	492	1.16 (0.99 to 1.35)	0.07	154	313	0.95 (0.78 to 1.16)	0.62
+ BMI	323	492	1.20 (1.02 to 1.40)	0.03	154	313	0.97 (0.79 to 1.18)	0.73
+ Smoking	323	492	1.16 (0.99 to 1.36)	0.07	154	313	0.93 (0.77 to 1.14)	0.49
+ Time of sampling	323	492	1.14 (0.96 to 1.34)	0.13	154	313	0.99 (0.81 to 1.21)	0.90
Adjusted	323	492	1.19 (1.01 to 1.41)	0.04	154	313	0.99 (0.80 to 1.22)	0.92
Sampling time restricted to 0700h -1100h:								
Unadjusted	268	396	1.19 (0.91 to 1.43)	0.06	45	89	1.21 (0.80 to 1.83)	0.36
+ BMI	268	396	1.26 (1.04 to 1.53)	0.02	45	89	1.23 (0.81 to 1.87)	0.33
+ Smoking	268	396	1.19 (0.99 to 1.44)	0.06	45	89	1.16 (0.76 to 1.76)	0.50
+ Time of sampling	268	396	1.22 (1.00 to 1.48)	0.04	45	89	1.17 (0.76 to 1.79)	0.48
Adjusted	268	396	1.31 (1.07 to 1.60)	0.01	45	89	1.13 (0.72 to 1.76)	0.59

OR, odds ratio; CI, confidence intervals; p, p value. All models included the matching variables of age; for VIP, MONICA and MSP, all models included the matching variables of sex, study, and baseline assessment date. Adjusted models also included BMI, smoking and time of sampling in the regression models. Analyses were repeated restricted to individuals with blood sampling time between 0700h and 1100h.

Table S3. Effect of including each confounder one-at-a-time on the associations of plasma cortisol with CVD in the imputed dataset of the combined VIP, MONICA and MSP cohort

	VIP, MONICA and MSP			
	Cases	Controls	OR (95% CI)	P
All sampling times included:				
Unadjusted	905	1717	1.00 (0.91 to 1.09)	0.91
+ BMI	905	1717	1.03 (0.94 to 1.13)	0.53
+ Smoking	905	1717	1.01 (0.92 to 1.10)	0.81
+ Time of sampling	905	1717	1.00 (0.91 to 1.11)	0.95
Adjusted	905	1717	1.06 (0.96 to 1.17)	0.24
Sampling time restricted to 0700h - 1100h:				
Unadjusted	702	1109	1.05 (0.94 to 1.17)	0.39
+ BMI	702	1109	1.10 (0.98 to 1.23)	0.12
+ Smoking	702	1109	1.06 (0.95 to 1.19)	0.30
+ Time of sampling	702	1109	1.05 (0.94 to 1.18)	0.41
Adjusted	702	1109	1.12 (0.99 to 1.26)	0.07

OR, odds ratio; CI, confidence intervals; p, p value. All models included the matching variables of age, sex, study and baseline assessment date. Analyses were repeated restricted to individuals with blood sampling time between 0700h and 1100h.

Table S4. Missing data in the VIP, MONICA and MSP cohort

Variable	Missing, n (%)
Plasma cortisol	0 (0)
Sampling time	1371 (52.3)
BMI	69 (2.6)
Smoking	97 (3.7)
Sex	0 (0)
Age	0 (0)
Survey date	0 (0)
Cohort	0 (0)
Fasting glucose	266 (10.1)
Leptin	42 (1.6)

BMI, body mass index.

Table S5. Associations with missing sampling time in the VIP, MONICA and MSP cohort

	No missing sampling time (n=1251)	Missing sampling time (n=1371)	p
Cortisol, nmol/l	528 (185)	524 (187)	0.59
Age, years	54.5 (7.3)	54.2 (8.3)	0.43
Male	873 (70)	1018 (74)	0.01
BMI, kg/m^2	26.5 (3.9)	26.1 (3.6)	0.002
Smoking	291 (24)	238 (25)	0.72
Case-control cohort			
Castro1	152 (12)	130 (9)	
Castro2	474 (38)	318 (23)	
FIA1	90 (7)	100 (7)	
FIA2	535 (43)	823 (60)	<0.001
Case (MI or stroke)	445 (36)	460 (34)	0.28
MI	230 (52)	306 (67)	<0.001
Ischemic stroke	178 (83)	128 (83)	0.94
Survey Date, days (SD)	12139 (838)	11891 (943)	<0.001
Fasted >8 hours	1000 (80)	665 (49)	<0.001
HDL cholesterol, nmol/l	1.40 (1.39)	1.27 (0.36)	0.10
Total cholesterol, nmol/l	6.29 (1.26)	6.03 (1.29)	0.81
Fasting glucose, nmol/l	5.55 (1.46)	5.36 (1.24)	0.0006
Postload glucose, nmol/l	6.75 (1.99)	6.62 (2.10)	0.10
Hypertension	660 (59)	666 (55)	0.07
Leptin, nmol/l	9.49 (9.40)	8.20 (7.92)	0.0002

BMI, body mass index; MI, myocardial infarction; SD, standard deviation; p, p value. For continuous variables the mean and SD are presented; for binary variables the number and percentage are presented. Castro1, Castro2, FIA1 and FIA2 are case-control studies within the VIP, MONICA and MSP cohort.

Table S6. Variables used in multivariable imputation models in the VIP, MONICA and MSP cohort

Variable	Type of variable	Model used to predict missing data in this variable	Classification of variable to predict missing data in other variables
Case	Binary	N/A no missing	Binary
Cortisol	Continuous	N/A no missing	Continuous
Sex	Binary	N/A no missing	Binary
Age	Continuous	N/A no missing	Continuous
Survey date	Continuous	N/A no missing	Continuous
Cohort	Categorical	N/A no missing	Categorical
Smoking	Binary	Logistic regression	Binary
BMI	Continuous	Linear regression	Continuous
Sampling time	Continuous	Linear regression (truncated lower limit of 0)	Continuous
Log transformed fasting glucose	Continuous	Linear regression	Continuous
Log transformed leptin	Continuous	Linear regression	Continuous

BMI, body mass index.

Table S7. Distributions of imputed variables in the imputed datasets and in the observed data (with no imputation) in the VIP, MONICA and MSP cohort

	% data imputed	Distribution Mean (SD) for continuous variables % for categorical variables	
		Imputed datasets	Observed (with no missing) dataset
Sampling time (minutes from 0700h)	52.3	144.9 (113.9)	129.0 (103.4)
BMI (kg/m^2)	2.6	26.3 (3.8)	26.3 (3.8)
Smoking	3.7	24.7	24.5
Fasting glucose	10.1	1.67 (0.19)	1.67 (0.19)
Leptin	1.6	1.84 (0.80)	1.84 (0.80)

BMI, body mass index.

Table S8. Association of plasma cortisol with CVD in the imputed dataset of the VIP, MONICA and MSP cohort

	VIP, MONICA and MSP			
	Cases	Controls	OR (95% CI)	p
Unadjusted	905	1717	1.00 (0.91 to 1.09)	0.91
Adjusted	905	1717	1.06 (0.96 to 1.17)	0.24
Unadjusted and 0700h-1100h	702	1109	1.05 (0.94 to 1.17)	0.39
Adjusted and 0700h-1100h	702	1109	1.12 (0.99 to 1.26)	0.07

OR, odds ratio; CI, confidence intervals; p, p value. All models included the matching variables of age, sex, study, and baseline assessment date. Adjusted models also included BMI, smoking and time of sampling in the regression models. The analyses using the imputed data include 2622 participants. Analyses were repeated restricted to individuals with blood sampling time between 0700h and 1100h for which sample sizes vary between 1811 and 1958.

Table S9. Case classification and covariates included in the multivariable regression of prospective studies meta-analysis

Study	Outcome	Case classification	Covariates included in regression model
VIP, MONICA and MSP[3,4]	Fatal CVD	ICD 8 and 9 codes: 414 and 798–799 ICD 10: I25 and R96–99	Age, sex, study, baseline assessment date, smoking, BMI and time of sampling
	Non-fatal CVD	ICD 8 and 9 codes: 410-413 and 430-438 ICD 10 codes: I20-I24 and I60-69	
BWHHS[20]	Fatal CHD	ICD10 codes: I20-I25, I51.6	Age, smoking, BMI and time of sampling
	Non-fatal CHD	MI (defined according to WHO criteria), first diagnosis of angina or coronary artery by-pass or angioplasty.	
Caerphilly[8]	Fatal IHD	ICD-9 codes: 410 to 414	Age, smoking, adult social class, alcohol consumption, height, FEV1/height^2, fibrinogen, white cell count
	Non-fatal IHD	ICD-9 codes: 410 to 414	
Vietnam Experience Study[9]	Fatal CVD	ICD-9 codes: 390–434 and 436–448 ICD-10 codes: I00–I78	None

ICD, International Classification of Disease

Table S10. Leave one out meta-analysis of prospective multivariable regression association of morning plasma cortisol with cardiovascular disease

Excluded study	OR (95% CI)
VIP, MONICA and MSP	1.13 (1.01 to 1.27)
BWHHS	1.21 (1.04 to 1.39)
Caerphilly	1.31 (1.11 to 1.53)
Vietnam	1.16 (1.04 to 1.29)
D+L pooled estimate	1.18 (1.06 to 1.31)

OR, odds ratio; CI, confidence interval; D+L, DerSimonian and Laird.

Table S11. Association of the genetic variants comprising the instrumental variable for morning plasma cortisol used in the Mendelian randomization analyses with potential confounders included in multivariable regression models in the VIP, MONICA and MSP cohort

	Age, years (95% CI)	Sex (95% CI)	Survey date, days (95% CI)	Cohort (95% CI)	BMI (95% CI)	Sampling time, minutes (95% CI)	Smoking (95% CI)
rs12589136	-0.27 (-0.81 to 0.28)	-0.08 (-0.23 to 0.08)	21.69 (-40.08 to 83.46)	0.04 (-0.04 to 0.11)	-0.20 (-0.47 to 0.06)	-1.76 (-11.91 to 8.39)	0.10 (-0.06 to 0.26)
rs2749529	-0.20 (-0.63 to 0.24)	-0.03 (-0.15 to 0.10)	29.90 (-18.91 to 78.71)	0.05 (-0.02 to 0.11)	-0.02 (-0.23 to 0.19)	-0.31 (-8.61 to 7.98)	0.06 (-0.07 to 0.19)
rs11621961	0.05 (-0.40 to 0.49)	0.01 (-0.11 to 0.14)	26.95 (-23.54 to 77.43)	-0.03 (-0.09 to 0.03)	-0.03 (-0.24 to 0.19)	-5.77 (-14.15 to 2.60)	-0.03 (-0.16 to 0.11)
Fixed-effects (IV pooled ES)	-0.13 (-0.39 to 0.14)	-0.02 (-0.10 to 0.05)	26.82 (-3.69 to 57.33)	0.02 (-0.02 to 0.06)	-0.07 (-0.20 to 0.06)	-2.70 (-7.80 to 2.40)	0.04 (-0.04 to 0.12)
Random-effects (D+L pooled ES)	-0.13 (-0.39 to 0.14)	-0.02 (-0.10 to 0.05)	26.82 (-3.69 to 57.33)	0.02 (-0.03 to 0.07)	-0.07 (-0.20 to 0.06)	-2.70 (-7.80 to 2.40)	0.04 (-0.04 to 0.12)

CI, confidence interval; IV, inverse variance; ES, effect size; D+L, DerSimonian and Laird. Effect estimates are the difference in means per allele associated with higher morning plasma cortisol

Table S12. Association between the genetic instrumental variable for morning plasma cortisol with morning plasma cortisol and potential confounders in publicly available GWAS consortia

Outcome	Consortium	Year	Effect estimate	LCI	UCI	p
Morning plasma cortisol	CORNET	2014	0.090	0.070	0.100	6·05e-28
Ever vs never smoked	TAG	2010	-0.009	-0.024	0.006	0.263
Cigarettes smoked per day	TAG	2010	-0.106	-0.210	-0.001	0.047
Total cholesterol	GLGC	2013	-0.006	-0.012	0.000	0.054
HDL cholesterol	GLGC	2013	-0.002	-0.008	0.004	0.489
LDL cholesterol	GLGC	2013	-0.007	-0.013	0.000	0.042
Triglycerides	GLGC	2013	0.003	-0.003	0.009	0.305
Fasting glucose	MAGIC	2010	-0.004	-0.008	0.001	0.140
2hr glucose	MAGIC	2010	0.003	-0.021	0.026	0.828
Type 2 diabetes	DIAGRAM	2014	0.019	0.003	0.035	0.021
Waist-to-hip ratio	GIANT	2015	0.005	-0.001	0.010	0.092
Overweight	GIANT	2013	-0.013	-0.025	-0.002	0.019
Weight	GIANT	2013	-0.007	-0.016	0.001	0.068
Waist circumference	GIANT	2015	0.002	-0.003	0.007	0.486
Obesity class 1	GIANT	2013	-0.010	-0.026	0.005	0.184
Obesity class 2	GIANT	2013	-0.001	-0.025	0.022	0.907
Obesity class 3	GIANT	2013	-0.002	-0.046	0.042	0.921
Body mass index	GIANT	2015	0.000	-0.004	0.005	0.874
Body fat	NA	2016	0.004	-0.002	0.011	0.204

LCI, 95% lower confidence interval; UCI, 95% upper confidence interval; HDL, high density lipoprotein; LDL, low density lipoprotein. Effect estimates are either the log Odds ratio (for binary outcome) or mean difference (for continuous outcome) from a random-effects meta-analysis. If multiple studies exist, the association if from the largest sample in a European population.

Table S13. Association of morning plasma cortisol on CHD from alternative two-sample Mendelian randomization approaches

Method	OR (95% CI)
Weighted mode	1·06 (0·94 to 1·19)
Maximum likelihood	1·06 (0·98 to 1·15)
Inverse variance weighted	1·06 (0·98 to 1·15)
Weighted median	1·06 (0·96 to 1·17)
MR-Egger – slope; intercept	0·80 (0·43 to 1·49); 0·03, se 0·03, p=0·53

OR, odds ratio; CI, confidence interval; MR, Mendelian randomization; se, standard error; p, p value.

Table S14. Association of morning plasma cortisol on CHD adjusting for possible risk factors from two-sample multivariable Mendelian randomization analyses

Exposures	No. of SNPs	OR	LCI	UCI	p
Morning plasma cortisol	3	1.04	0.94	1.15	0.44
Type 2 Diabetes	46	1.09	1.06	1.12	9.89E-13
Morning plasma cortisol	3	1.09	0.97	1.22	0.16
Overweight	20	1.20	1.14	1.26	1.68E-11
Morning plasma cortisol	3	1.04	0.73	1.48	0.83
Cigarettes per day	6	0.98	0.95	1.00	0.09
Morning plasma cortisol	3	1.03	0.93	1.14	0.56
LDL Cholesterol	303	1.47	1.41	1.52	2.33E-97

SNP, single nucleotide polymorphism; OR, odds ratio; LCI, 95% lower confidence interval; UCI, 95% upper confidence interval; p, p value; LDL, low density lipoprotein. Morning plasma cortisol from CORNET consortium (n=12,597). Overweight (BMI) from GIANT consortium (cases=93,015, controls=65,840). Cigarettes smoked per day from TAG consortium (n=68,028). LDL cholesterol from GLGC (n=173,082).

Supplemental Figure

Figure S1. Funnel plot of log odds ratio (logOR) against the standard error of log odds ratio (se logOR) to assess potential small study bias in the meta-analysis of prospective studies